Age-specific Oncogenesis: The Genetics of Cancer Susceptibility

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Cancer is considered to be a multifactorial disease in which a host cell is transformed from normal to malignant as a result of complex interactions of external (environmental) stimuli and cancer-predisposing or cancer-suppressing genes. Although certain chemical carcinogens and ionizing radiation are known to cause specific alterations at the level of the gene, other correlations are less clear. Not infrequently, cancer is found to aggregate in families in an apparently nonrandom fashion. It has been through the study of such families that our understanding of the genetic events leading to cancer has developed. Both common and rare tumors may occur together in familial-cancer families. Frequently, tumors occur at an earlier age than one would expect in the general population; often, multiple tumors of different organs develop in a particular affected family member. Recent advances in the genetics of familial cancer syndromes have led to the possibility to perform genetic testing on unaffected relatives who might carry a genetic defect that predisposes them to cancer. Complex ethical, social, and legal implications arise from these new technical advances. — Environ Health Perspect 103(Suppl 6):37–39 (1995)

Key words: familial cancer, Li-Fraumeni syndrome, predictive genetic testing

Introduction

For many cancers, etiologic environmental associations are well documented. The link between smoking and lung cancer is well described. It is suspected that dietary practices have much to do with the global variation in the incidence of carcinomas of the stomach and colon. The hepatitis B virus and exposure to aflotoxin may be major etiologic agents for primary liver carcinoma, and a variety of etiologic associations have been causally associated with breast cancer. It will be noted, however, that the majority of those cancers associated with exposures to environmental agents are typically of adult onset. Weaker epidemiologic associations of ionizing radiation and cancers of the hematopoietic systems and brain tumors, as well as discrepant observations linking electromagnetic fields with leukemogenesis in children have been made. In most instances, however, a direct correlation between these exposures and cancer development are difficult to make.

Nonrandom aggregations of cancer have been recognized to occur since the middle of the last century. Although

almost every type of cancer has been reported to occur in a familial form, evidence of hereditary and familial influences exist in only a few percent of cases (1). The actual fraction of human cancers that are due to genetic and familial factors is not known; however, more than 100 single-gene disorders, including autosomal dominant, recessive, and X-linked conditions have been associated with a high risk of cancer development. Some of these phenotypes are represented primarily by the development of cancer clustering in families, whereas in others such as ataxia-telangectasia, cancer appears to occur as a secondary event. In fact, as it turns out, the genetic events leading to cancer development in this disorder may not be dissimilar from those associated with molecular carcinogenesis in sporadic malignancies. Certain cancers, such as retinoblastoma, a rare eye tumor of childhood, appear to arise primarily through inherited (germline) genetic alterations that are passed from parent to child, while others, including cancers of the lung, bladder, and oral cavity develop as a result of interactions between intracellular acquired (somatic) genetic changes induced by external environmental signals.

Epidemiologic studies have demonstrated that some people carry in their genes a predisposition to develop cancer. Often this genetic predisposition leads to an increased likelihood of suffering from a specific cancer or group of cancers compared to the general population. Although individuals with well-defined cancer family

syndromes account for only a small minority (perhaps 0.1% of all people with cancer), those patients belonging to families with cancer where heredity plays some role may account for up to 10% of all cancer. The most characteristic feature of hereditary cancers is the tendency for their early age of onset. In addition, it is not at all unusual to find affected children in these kindreds. In addition to the significant questions surrounding potential detection of genetic predisposition to cancer in individuals at high risk, the study of hereditary cancers and cancer families has led to the detection of a class of genes critical both in carcinogenesis and normal development (2).

Faulty regulation of cellular growth and differentiation leads to neoplastic transformation and tumor initiation. Many inappropriately activated growth-potentiating genes, or oncogenes, have been identified through the study of RNA tumor viruses and the transforming effects of DNA isolated from malignant cells. Mutations in oncogenes tend to occur in one of the two alleles of the gene, and act in a dominant manner to the wild-type (normal) allele. These are, in effect, "gain of function" mutations that constitutively or permanently signal the cell to divide. Activated dominant oncogenes, however, do not themselves readily explain a variety of phenomena related to transformation and tumor formation. Among these are suppression of tumorigenicity by fusion of malignant cells with their normal counterparts, tumor-associated specific chromosome deletions, and the existence of hereditary

forms of cancer, as described above. In fact, although mutations in oncogenes appear to arise spontaneously in somatic tissues over the lifetime of the organism, naturally occurring inherited forms of these mutations are not known.

Comparisons between the frequencies of familial tumors and their sporadic counterparts led Knudson to suggest that familial forms of some tumors could be explained by constitutional mutations in growth-limiting genes. The resulting inactivation of these genes would facilitate cellular transformation. Inactivations of these growth-limiting, or tumor suppressor, genes are the result either of mutations in both alleles or a mutation in one allele followed by a loss of, or a "reduction to homozygosity," in the second. Unlike the dominant oncogenes, mutant tumor suppressor genes may be present in either germ cells or somatic cells. In the former, they may arise spontaneously in the gamete or be transmitted from generation to generation within a family. Although studies have located the chromosomal sites of many putative tumor suppressor genes, only a few have been isolated to date. These include the retinoblastoma susceptibility gene (*RB1*), the Wilms tumor gene (*WT1*), *p53* in the Li-Fraumeni family cancer syndrome, genes associated with the development of colon carcinoma [adenomatous polyposis coli (APC), mutated in colon cancer (MCC)], and the gene associated with neurofibromatosis. Although the function of the protein encoded by each of these genes differs, they all share the properties associated with suppression of cell growth and proliferation.

The paradigm for early age of onset of cancer in extended pedigrees is the Li-Fraumeni syndrome (*3*). This disorder, first characterized in 1969, is now classically represented by the presence of a proband with sarcoma under the age of 45, a first-degree relative who develops a sarcoma before the age of 45 years, and a second first-degree relative with cancer of any type diagnosed under the age of 45 years. Other frequently occurring tumors include breast cancer, acute leukemias, brain tumors, carcinomas of the adrenal cortex, and osteosarcomas. Often it is found that affected family members who survive their first tumor go on to develop a second malignancy that is different in its histopathology from the first. It is very common to discover several tumors in different affected family members that occur at ages earlier than expected for the general population

(*4*). Heritable germline mutations of the *p53* tumor suppressor gene have been described in probands of Li-Fraumeni syndrome families and both affected and young unaffected relatives (*5,6*). In addition, occasional germline *p53* mutations have been described in patients not belonging to Li-Fraumeni kindreds but who have multifocal osteogenic sarcoma, multiple primary malignancies, and to a very much lesser degree, breast cancer. Several studies are ongoing in other populations of cancer patients to determine the genetic heterogeneity of Li-Fraumeni syndrome, and the high-risk cancer populations likely to harbor a genetic predisposition to the cancers they develop.

The very high probability of developing cancer in individuals, and in particular children, who carry germline alterations of tumor suppressor genes has led to the possibility of predictive genetic testing in unaffected relatives. It is now technically feasible to perform such testing in many molecular biology laboratories worldwide. However, with the imminent identification of many more genes for hereditary diseases, including cancer, many of which will directly affect children, the proper use of the genetic information in both individuals and the population is a matter of growing concern. Many issues, such as autonomy, confidentiality, and nondiscrimination, are generic to testing for any heritable disease. For adult-onset genetic disorders such as Huntington's or Alzheimer's disease, the issue of testing children is less frequently found to be at issue. However, for diseases such as cancer, for which primary preventive measures may be available, predictive testing of children raises important concerns (*7,8*).

One of the most widely discussed and evaluated testing "programs" has been that of *p53* testing in high-risk patients, including those who belong to classic Li-Fraumeni families, those who belong to families with cancer histories resembling this syndrome, and individuals who are relatives of patients with characteristic features of the syndrome in the absence of a family history of cancer. These risk groups, as examples of children and young adults who might benefit or suffer from such testing, are discussed in more detail elsewhere in the symposium.

I present here recommendations that should be considered in the development of predictive genetic testing policies for cancer in children and young adults (*9*):
• Predictive testing for germline muta-

tions of genes associated with cancer predisposition should be performed only in pilot research programs with the availability of knowledgeable psychosocial, genetic, medical, and oncologic counseling, as well as established molecular screening laboratories with expertise in the interpretation of the biological significance of observed genetic alterations.
• Within the above research settings, predictive testing should be offered only to close relatives of cancer patients in whom a germline gene mutation has been previously identified. Such testing should be undertaken only after appropriate counseling on the benefits and limitations of testing (both technical and interpretive) has been provided.
• Predictive genetic testing on cancer patients or the general population should not be undertaken outside defined research settings; the harmful potential of such testing far outweighs the benefits. Furthermore, the carrier rate for most of the currently isolated cancer-predisposing genes is demonstrably low.
• It is critical that appropriate counseling be given to carriers of mutant genes and their relatives regarding the seeking of early medical attention for signs and symptoms of cancer and pursuit of healthy lifestyle.
• Further study of the impact of predictive testing on children within the limited research settings outlined above should be carried out.

There are many gaps in our knowledge of the role of genetic predisposition in cancer development, and many drawbacks of predictive testing as it is currently available. Nonetheless, the possibility of reducing the marked loss of human potential resulting from the death of a child or young adult makes pilot research efforts for early intervention in carriers of germline mutations of cancer-predisposing genes worthwhile. Further studies into the development of more accurate testing procedures, understanding of the effect of germline mutations on cell transformation and tumor formation, and perhaps the development of animal models will continue to be important. In addition, studies of evaluation of cancer risk notification addressing this process, the impact of knowledge, attitudes, emotions, and disease and health status outcomes are required (*10*). Ultimately, one would hope that these studies lead through screening to the early detection and successful treatment of cancer in children and young adults.

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